REMARKS

This application has been reviewed in light of the Final Office Action dated April 13, 2011. Claims 1, 3, 6-16 and 19-24 are presented for examination, of which Claims 1 and 22 are in independent form. Claims 1 and 22 have been amended. Claims 3 and 25 have been cancelled, with claim 25 withdrawn from consideration as being directed to a non-elected invention. Favorable reconsideration is requested.

Claims 1, 3, 6-16, 19-20 and 22-24 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 3,993,072 (Zaffaroni), U.S. Patent No. 2,962,023 (Chappaz et al.) and U.S. Patent No. 5,972,372 (Saleh et al). Applicants respectfully traverse the rejection.

Claim 1 has been amended to recite an intravaginal drug delivery device for administration into a vaginal environment, the device comprising at least one reservoir, the at least one reservoir containing at least one pharmacologically active agent or a prodrug thereof, dispersed in a hydrophobic elastomeric polymer; and a sheath discontinuously surrounding the at least one reservoir so as to define one or more holes or openings, each hole or opening extending through the sheath to the at least one reservoir, wherein each hole or opening is substantially cylindrical with a diameter in the range of about 0.5 to 6.5 mm, so that, in use, at least part of the at least one reservoir is directly in contact with the vaginal environment and the total surface area of the reservoir in contact with the vaginal environment through the one or more holes or openings, when in use, is in a range of 1 to 750mm^2, wherein the sheath is impermeable to the at least one pharmacologically active agent or the prodrug thereof and wherein the at least one pharmacologically active agent or the prodrug thereof is released from the hydrophobic elastomeric polymer directly in contact with the vaginal environment.

Basis for the amendment can be found throughout the specification, particularly at paragraph [0011], which describes that at least part, but not all, of the reservoir is directly exposed to the vaginal environment while in use; paragraph [0013], which describes the provision of one or more, optionally at least two, further optionally at least three or at least five, holes or openings; and paragraph [0086], which discloses that the drug is released from the reservoir by diffusion of the drug through the reservoir carrier system.

Prior to discussing the merits of the rejection, Applicants believe it would be helpful to highlight the presently claimed invention. The present invention is concerned with the delivery of at least one pharmacologically active agent or a prodrug into a vaginal environment. As described at paragraph [0008], various physicochemical parameters control the rate of release of a pharmacologically active agent (drug) from an intravaginal drug delivery device having an outer, rate-controlling sheath.

The present invention seeks to provide a daily release rate of the drug in the order of milligrams per day, as described at paragraph [0009], and acknowledges, at paragraph [0086], that factors governing release from the intravaginal drug delivery devices of the present invention are the solubility of the drug in the reservoir carrier system, the solubility of the reservoir carrier material and/or reservoir excipient in vaginal fluid, and the surface area of the reservoir exposed to the vaginal environment.

By providing holes or openings with a diameter in the range of about 0.5 to 6.5 mm, so that, in use, the total surface area of the reservoir in contact with the vaginal environment is in a range of 1 to 750mm^2, the present invention permits a daily release rate of the drug in the order of milligrams per day, but without allowing the reservoir to exude from the device. The

present invention provides a hydrophobic elastomeric polymer, which is purposely permitted to be directly in contact with the vaginal environment in a range of 1 to 750mm^2 to permit influx of fluid from the vaginal environment and the active release of drug, thereby moving away from the teachings of the prior art to provide a sheath of lower permeability for passive diffusion of the drug, hole size sufficient to allow the reservoir to exude, and provision of a sheath fully surrounding the reservoir as the drug-release rate-controlling step for releasing drug over a prolonged period of time. Applicants submit that the present invention is not disclosed or suggested by the prior art of record.

The Examiner suggests that, with respect to Claim 1, Zaffaroni discloses the pore structure of the sheath further includes continuous pores and, therefore, the sheath is considered to discontinuously surround the at least one reservoir so as to define at least one hole or opening. Applicant respectfully disagrees.

Zaffaroni discloses a drug delivery device comprising (a) a wall formed of a microporous material having a plurality of micropores with a pore size of 10 angstroms to 100 microns and formed with diffusional conduits through the wall, and (b) a reservoir surrounded by the wall comprising a solid carrier containing dissolved and undissolved drug with the carrier permeable to the passage of dissolved drug by diffusion.

More particularly, Applicants maintain that Zaffaroni teaches a microporous wall, which surrounds the reservoir, but makes no specific disclosure of each hole or opening is substantially cylindrical with a diameter in the range of about 0.5 to 6.5 mm. Although Zaffaroni teaches that the rate of passage of drug is generally dependent on the size of the pores, as highlighted by the Examiner; there is no teaching in Zaffaroni that each hole or opening has a

diameter in the range of about 0.5 to 6.5 mm. Certainly, Zaffaroni only teaches a pore size of 10 angstroms to 100 microns.

In the description, Zaffaroni teaches that release through the pores of the wall is the drug-release rate-controlling step for releasing drug over a prolonged period of time from the device to produce the desired results. Specifically, Zaffaroni teaches, at column 1, lines 29-30, that the permeability of the microporous wall to the drug is lower than the permeability of the solid carrier to the drug so that, as is taught at column 3, lines 63-65, the passage of drug through the micropores of the wall is the rate determining step for drug release from the drug delivery device.

Zaffaroni is concerned with a unique construction and operation of a device and its ability to transfer drug to a recipient or to a drug receptor site. It is specifically taught, at the paragraph bridging column 8 and 9, that the device can be viewed as a single unit constructed device comprising two structures acting in concert for effective drug administration to a host. Applicant respectfully highlights to the Examiner that, essentially, Zaffaroni discloses a drug-containing reservoir and a microporous sheath fully surrounding the reservoir, and through which the drug must diffuse to reach the recipient, the drug diffusion being controlled by the microporous sheath in a passive manner (as is described at column 5, lines 22-29); whereas the present invention provides that the sheath is impermeable to the at least one pharmacologically active agent or the prodrug thereof, and the drug-containing reservoir is purposely in direct contact with the vaginal environment through the one or more holes or openings, each having a diameter in the range of about 0.5 to 6.5 mm, and having a total surface area in a range of 1 to 750mm^2.

Applicant further submits that the provision of one or more holes or openings, each having a diameter in the range of about 0.5 to 6.5 mm, and having a total surface area in a range of 1 to 750mm^2 in the instant invention permits the influx of fluid from the vaginal environment, in an amount sufficient to allow release of the at least one pharmacologically active agent from the hydrophobic elastomeric polymer in which it is dispersed.

Specifically, in contrast to Zaffaroni, the instant invention provides that passage of the at least one pharmacologically active agent from the hydrophobic elastomeric polymer is the rate-determining step for drug release from the drug delivery device. By purposely providing that the total surface area of the reservoir in contact with the vaginal environment through the one or more holes or openings, when in use, is in a range of 1 to 750mm^2, the at least one pharmacologically active agent is released from the hydrophobic elastomeric polymer directly in contact with the vaginal environment in an active manner, by permitting influx of fluid from the vaginal environment; which fluid acts by detaching individual molecules of the dispersed active drug(s) from their crystal lattice within the hydrophobic elastomeric polymer, whereby the at least one pharmacologically active agent is released from the hydrophobic elastomeric polymer through direct contact with the vaginal environment.

As is taught at paragraph [0052] of the Application as filed, and column 3, lines 53-55 of Zaffaroni, in the device of Zaffaroni, before release can occur, individual molecules of the dispersed active drug(s) within the reservoir must first detach themselves from their crystal lattice, dissolve into the surrounding reservoir carrier system, diffuse to the surface of the reservoir and then diffuse through the sheath to the surface of the device. Once at the surface, the drug should then exhibit some aqueous solubility in order to partition into the aqueous diffusion layer consisting primarily of vaginal fluid, from which it then partitions into and across vaginal

epithelium and, hence, into the systemic circulation. The instant invention overcomes these deficiencies by providing that the total surface area of the reservoir in contact with the vaginal environment through the one or more holes or openings, when in use, is in a range of 1 to $750mm^2$, thereby allowing influx of fluid from the vaginal environment, in an amount sufficient to allow release of the at least one pharmacologically active agent from the hydrophobic elastomeric polymer in which it is dispersed.

Accordingly, the present invention moves away from the teaching of Zaffaroni to provide a microporous sheath having permeability to the drug that is lower than the permeability of the solid carrier to the drug for the passive diffusion of drug. In fact, in contrast with the teaching of Zaffaroni, in the present invention, drug release by the reservoir is the rate-controlling step for releasing drug over a prolonged period of time from the device; which is achieved by the use of a hydrophobic elastomeric polymer, which is purposely permitted to be directly in contact with the vaginal environment in a range of 1 to $750mm^2$ to permit influx of fluid from the vaginal environment and the active release of drug.

Accordingly, Applicant submits that the claimed invention would not have been suggested by Zaffaroni to a person of ordinary skill in the art.

The Examiner suggests that Chappaz teaches the diffusion rate of and the amount of drug that is to be dispensed from the device is dependent in the number of holes in the sheath. Applicant submits that Chappaz discloses a medicator comprising a container having walls of solid material, the walls having numerous perforations, whereby medicament enclosed within the hollow interior as a reservoir passes outward through the perforations. Specifically, at column 4, lines 8-10, Chappaz discloses that the medicator is filled with a medicating cream which melts at body temperature and exudes slowly but continuously through the perforations.

Applicant submits that Chappaz makes no specific disclosure that each hole or opening is substantially cylindrical with a diameter in the range of about 0.5 to 6.5 mm, so that, in use, the total surface area of the reservoir directly in contact with the vaginal environment through the one or more holes or openings, when in use, is in a range of 1 to 750mm^2, and wherein at least one pharmacologically active agent is released from the hydrophobic elastomeric polymer directly in contact with the vaginal environment. Specifically, Applicant maintains that the device of Chappaz is an applicator, and is not intended for the delivery of drugs, but is intended for the delivery of drug-containing substances, because the entire 'core' (in the form of a semi-solid formulation) is released through holes of the applicator, whereas, in the present application, the reservoir comprising the hydrophobic elastomeric polymer, in which the drug is dispersed, remains intact and in place. Only the drug is released into the vaginal environment. Accordingly, the present invention provides a controlled drug release by retaining the reservoir within the device, a result that would not be achievable by the device of Chappaz.

Thus, Chappaz does not overcome the deficiencies of Zaffaroni. There is no teaching made by either Chappaz or Zaffaroni that would motivate the skilled person to arrive at the present invention; particularly given that Chappaz teaches that the number and size of the perforations may be varied to allow the medicament (including the reservoir) to exude from the medicator. Clearly, Chappaz is concerned with dispensing drug (including the reservoir), and so teaches that amount of drug exuded is dependent on hole size. However, the present invention moves away from the teaching of Chappaz by providing holes or openings with a diameter, and total surface area directly in contact with the vaginal environment to allow influx of fluid from the vaginal environment in an amount sufficient to allow release of the at least one pharmacologically active agent from the hydrophobic elastomeric polymer in which it is

dispersed; but without allowing the reservoir to exude from the device. Applicant submits that a change in size and shape is not within the level of one of ordinary skill in the art in the face of a contradictory teaching. Accordingly, Applicant submits that the claimed invention is not rendered obvious by Chappaz in combination with Zaffaroni.

The Examiner suggests that Saleh teaches a polymer impregnated with drug that goes inside an outer sheath with holes. Applicant submits that Saleh describes a vaginal ring having a hollow internal channel capable of receiving a drug-containing core. However, there is no disclosure in Saleh that each hole or opening is substantially cylindrical with a diameter in the range of about 0.5 to 6.5 mm, so that, in use, the total surface area of the reservoir directly in contact with the vaginal environment through the one or more holes or openings, when in use, is in a range of 1 to 750mm^2, and wherein the at least one pharmacologically active agent released from the hydrophobic elastomeric polymer directly in contact with the vaginal environment.

Indeed, Applicant maintains that Saleh discloses, at page 3, lines 7-12, a sealant that may be used to separate the core from the exterior environment so as to prevent passage or diffusion of the drug from the core directly to the exterior environment. Moreover, Salah describes, at column 3, lines 53-55, a kit containing a sealant for sealing the hollow channel after positioning the drug-containing core therein. Saleh goes on to teach that the sealant is preferably a medical grade adhesive. Applicant submits that the device disclosed by Saleh is essentially a drug-containing reservoir surrounded by a drug-permeable sheath.

The Saleh device is taught to have a core, wherein no portion of the core is exposed to, or in contact with, the outer surface of the ring body (see column 6, lines 6-12). Specifically, Saleh teaches, at column 8, lines 57-64, that the channel is approximately half-filled with the sealant, followed by insertion of the core, which assures a firm, uniform contact

between the drug-containing core and the inner surface of the hollow channel; and that additional sealant is added and the excess, which is also squeezed from the open end of the channel, is removed while sealing the open end of the channel flush with the outer surface of the support.

There is no teaching in Saleh that the device has a sheath defining one or more holes or openings, each hole or opening extending through the sheath to the at least one reservoir, so that, in use, at least part of the at least one reservoir is directly in contact with the vaginal environment. In contrast, at column 6, lines 62-66, Saleh teaches minimising diffusion of the drug through the axial ends of the core. Saleh even discloses that, by ensuring that the core is not exposed to, or in contact with, the outer surface of the ring body, uniform drug release is achieved to circumvent nausea and vomiting resulting from an initial burst of drug.

Saleh fails to overcome the deficiencies of Zaffaroni, particularly given that both Zaffaroni and Saleh both teach the provision of a sheath to enclose the drug-containing reservoir, and ensure that the drug-containing reservoir does not come into contact with the recipient.

Moreover, Saleh does not overcome the deficiencies of Chappaz, given that Saleh teaches that the drug-containing reservoir is retained in the device to obtain a uniform drug release, whereas Chappaz teaches that the drug-containing reservoir should be exuded from the device to obtain a uniform drug release.

Accordingly, Applicant submits that the claimed invention is not rendered obvious by Saleh, in combination with Zaffaroni, and Chappaz.

In view of the foregoing remarks, favorable reconsideration and passage to issue is earnestly requested. Should the Examiner believe that issues remain outstanding, the Examiner is respectfully requested to contact Applicants' undersigned attorney in an effort to resolve such issues and advance the case to issue.

Applicants' undersigned attorney may be reached in our New York Office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address listed below.

Respectfully submitted,

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